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10/574,163	03/29/2006	Jin Liu	8028-005-US	4114

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EXAMINER	
AFREMOVA, VERA	
ART UNIT	**PAPER NUMBER**
1657	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/574,163	LIU ET AL.	
	Examiner	Art Unit	
	Vera Afremova	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10/22/2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-7,9,12-32,35-40 and 56-58* is/are pending in the application.

4a) Of the above claim(s) *35-40 and 56-58* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7,9 and 12-30* is/are rejected.

7)☒ Claim(s) *31 and 32* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *10/22/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-7, 9 and 12-32 are under examination in the instant office action.

Claims 8, 10, 11, 33, 34, 51-55 were canceled by applicants.

This application contains claims 35-40 and 56-58 drawn to invention(s) nonelected with traverse in the reply filed on 2/05/2008.A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Deposit

Deposit requirement for the cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565 has been met in papers field 10/22/2008.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 12-21, 23-25 and 28-30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 5,665,589 (Harris et al).

Claims are directed to a virally immortalized hepatocyte that is derived from normal liver cells, that is nontumorogenic, that produces therapeutic plasma proteins (TPPs) and that is stable in culture and not undergoing dedifferentiation in culture. Some claims are further drawn to hepatocyte that is derived from human liver cell, that comprises SV40 Tag DNA. Some

claims are further drawn to hepatocyte that retains hepatic functions including enzymatic activity or cytochrome P450 activity and ability to produce plasma proteins including albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing.

US 5,665,589 (Harris et al) discloses virally immortalized hepatocyte cell lines including cell lines THLE that are derived from human normal liver cell (abstract). The hepatocytes are immortalized with retroviral vector containing SV40 TAG gene and they are nontumorogenic (col. 2, lines 15-25). The cited hepatocytes have indefinite lifespan in vitro (col. 2, line 24) and, thus, they are stable in culture and not undergoing spontaneous dedifferentiation to the same degrees as intended for the presently claimed immortilized hepatocytes, particularly in view of the teaching that the cited cell lines are suitable for investigation of the control of differentiation upon treatment with compound that induce terminal differentiation (col. 2, lines 39-47). The cited hepatocytes produce therapeutic plasma proteins (col. 10, lines 20-27) including albumin, transferring and alpha-1 antitrypsin (same as inter-alpha-inhibitor proteins accordingly to the definitions of specification page 49, line 18). The cited hepatocytes retain enzymatic activity including cytochrome P450 (col. 1, line 19). Thus, the disclosed virally immortalized hepatocytes have the same characteristics and they posses the same metabolic functions as required by the instant claims. With respect to the claim 30 it is noted that this claim is directed to the intended use. The cited document suggests the use of immortalized hepatocytes in various assays including carcinogenesis and drug testing (col. 4, lines 20-25) and the cited virally immortalized hepatocytes have the same characteristics as the claimed hepatocytes. Therefore, the cited hepatocytes are reasonably

expected to be suitable for the same assays as encompassed by the claim 30.

Thus, US 5,665,589 (Harris et al) anticipates the claimed invention.

Claims 1, 4-7, 9-22 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by US 6,107, 043 (Jauregui et al).

Claims are directed to a virally immortalized hepatocyte that is derived from normal liver cells, that is nontumorogenic, that produces therapeutic plasma proteins (TPPs) and that is stable in culture and not undergoing dedifferentiation in culture. Some claims are further drawn to hepatocyte that comprises SV40 Tag DNA. Some claims are further drawn to the hepatocyte that has ability to be maintained in a generic serum free medium including "MFE" serum free medium. Some claims are further drawn to hepatocyte that retains hepatic functions including enzymatic activity or cytochrome P450 activity and ability to form acetaminophen conjugate. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing.

US 6,107, 043 (Jauregui et al) discloses virally immortalized mammalian hepatocytes cell lines I-V that derived from normal liver cells, that are nontumorogenic and that maintain differentiated liver-specific metabolic activity concurrent with proliferative activity (entire document including abstract and col. 13, lines 56-60) and, thus, they are "stable in culture and not undergoing dedifferentiation in culture" as required for the claimed hepatocyte. US 6,107, 043 (Jauregui et al) teaches that serum is not necessary for proliferation and for maintenance of metabolic functions of the immortilized hepatocyte cell lines (col. 3, lines 57-58) and thus, the cited hepatocytes have ability to be maintained in a generic serum free medium including the

presently claimed "MFE" serum free medium of unknown/uncertain particular composition. The cited hepatocytes retain hepatic functions including enzymatic activity or cytochrome P450 activity and ability to form acetaminophen conjugate (paragraph bridging col. 7 and col. 8). US 6,107, 043 (Jauregui et al) also teaches the use of immortalized hepatocytes in various assays including toxicology testing (col. 12, lines 41-67) and the cited virally immortalized hepatocytes have the same characteristics as the claimed hepatocytes. Therefore, the cited hepatocytes are reasonably expected to be suitable for the same assays as encompassed by the claim 30. Thus, US 6,107, 043 (Jauregui et al) anticipates the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-7, 9 and 12-30 are rejected under 35 U.S.C. 103(a) as being unpatentable over US 5,665,589 (Harris et al), US 6,107, 043 (Jauregui et al) in view of US 6,653,105 (Triglia et al).

Claims are directed to hepatocyte cell line that is a virally immortalized hepatocytes, that is derived from normal liver cell, that is nontumorogenic and produces therapeutic plasma proteins (TPPs). Some claims are further drawn to hepatocyte capable to grow in serum-free media. Some claims are further drawn to hepatocyte that is derived from human liver, that comprises SV40 Tag DNA, that retains enzymatic activity including cytochrome P450, that

produces albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins and clotting factors. Some claims are further drawn to indented use of hepatocyte in various assays including drug testing.

The cited US 5,665,589 (Harris et al) and US 6,107, 043 (Jauregui et al) are relied upon as explained above for the disclosure of virally immortalized hepatocytes that are derived from mammalian including human normal liver cells and immortalized with retroviral vector containing SV40 TAG gene. The cited US 5,665,589 (Harris et al) teaches that the immortalized hepatocyte cell lines THLE are nontumorogenic, retain enzymatic activity of normal hepatocytes including cytochrome P450 activity and they have ability to produces various therapeutic plasma proteins including albumin, transferring, alpha-1-antitrypsin or inter-alpha-inhibitor proteins.

US 5,665,589 (Harris et al) teaches that immortilized hepatocytes retained enzymatic activities and functions of normal hepatocytes but it is silent about their ability to form acetaminophen conjugates and to produce clotting factors.

However, US 6,107, 043 (Jauregui et al) teaches that mammalian virally immortalized hepatocytes that are derived from normal liver cells retain liver-specific functions of normal hepatocytes including ability to form acetaminophen conjugates.

Further, US 6,653,105 (Triglia et al) teaches production of serum proteins including albumin, antitrypsin and clotting factors as a liver-specific biological function of hepatocytes, thereby, providing a reasonable expectation in retention of these functions by virally immortilized human hepatocytes of US 5,665,589 (Harris et al).

The cited US 5,665,589 (Harris et al) is lacking particular disclosure about ability of

the immortalized hepatocytes to grow on a serum free media. However, US 6,107, 043 (Jauregui et al) teaches that serum is not necessary for proliferation and for maintenance of metabolic functions of mammalian immortilized hepatocyte cell lines (col. 3, lines 57-58). Furthermore, US 6,653,105 (Triglia et al) teaches generation of serum-free clonal cell lines from parent human hepatocytes obtained on serum-containing media. The cited patent teaches advantage of serum-free hepatocytes for harvesting bio-products or plasma proteins manufactured in serum-free environment that considerably reduces risk of harboring infectious agents (col. 2, lines 40-50).

Thus, it would be obvious to obtain or to adapt hepatocyte cell lines for growth in serum-free medium for the expected benefits in manufacturing bio-products free of infectious agents. Therefore, the claimed invention as a whole was clearly prima facie obvious, especially in the absence of evidence to the contrary. The claimed subject matter fails to patentably distinguish over the state art as represented be the cited references. Therefore, the claims are properly rejected under 35 USC § 103.

Response to Arguments

Applicant's arguments filed 10/22/2008 have been fully considered but they are not all found persuasive.

Deposit requirement for the cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565 has been met in papers field 10/22/2008.

Claim rejection under 35 U.S.C. 102(a) as being anticipated by the Xeno Tech publication (IDS reference; Xenotechniques. 2003. Vol. 1, No. 1, pages 1-11) has been withdrawn since this publication is not a prior art as presently argued (exhibit 1).

Claim rejection under 35 U.S.C. 102(a) as being anticipated by Mills et al. (IDS reference; Mills et al. "An HTS Assay for Induction of Enzymes and Transporters Using a Human Hepatocyte Clonal Line and RNA Detection," Drug Metab. Rev. 34 (Suppl. 2): 124 (2002)) has been withdrawn in view of applicants' Declaration filed 10/22/2008 attesting to the conception and reduction to practice of the claimed invention prior to the October 27, 2002 publication of the cited reference by Mills that discloses hepatocyte cell line Fa2N-4.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 5,665,589 (Harris et al) applicants appear to argue that the cited patent does not teach or suggest the essential features of the presently claimed immortalized hepatocytes because the cells disclosed in Harris (1) are not derived from a normal liver epithelial cell and (2) do not naturally produce endogenous therapeutic plasma proteins and 3) are not stable in culture and undergo dedifferentiation as evidenced at col. 10, lines 31-66 of US 5,665,589 (Harris et al) (response page 12-14). The reference has been reviewed and arguments are found lacking any persuasive basis. First, the cited US 5,665,589 (Harris et al) clearly states that the disclosed cell lines including cell lines THLE are derived from human normal liver cell (see abstract). Second, the cited hepatocytes produce therapeutic plasma proteins (col. 10, lines 20-27) including albumin, transferring and alpha-1 antitrypsin. Third, the cited hepatocytes have indefinite lifespan in *vitro* (col. 2, line 24) and, thus, they are stable in culture and not undergoing spontaneous dedifferentiation to the same degrees as intended for the presently claimed immortilized

hepatocytes, particularly in view of the teaching that the cited cell lines are suitable for investigation of the control of differentiation upon treatment with compound that induce terminal differentiation (col. 2, lines 39-47). Moreover, the disclosure at the col. 10 that is argued clearly indicates that the THLR cells represent a population with a differentiation grade between oval cells and hepatocytes (col.10, lines 53-54), thus, confirming that cells are stable enough to establish/evaluate their developmental stage.

With regard to the claim rejection under 35 U.S.C. 102(b) as being anticipated by US 6,107, 043 (Jauregui et al) applicants argue (response page 14) that Jauregui does not disclose or suggest immortalized hepatocytes that are stable and not undergoing dedifferentiation because Jauregui discloses cells that undergo cell death in circumstances which lead to the expression of liver-specific proteins as evidenced at column 11, lines 37-41. The reference has been reviewed and arguments are found lacking any persuasive basis because at column 11, lines 37-41 the cited reference clearly teaches various assay of metabolic inducers by using the immortalized hepatocytes cell lines within the meaning of the instant claim 30, drawn to identification of agents that induce terminal differentiation or cell death. US 6,107, 043 (Jauregui et al) clearly teaches that the immortalized hepatocytes maintain differentiated liver-specific metabolic activity concurrent with proliferative activity (col. 13, lines 56-60) and, thus, they are "stable in culture and not undergoing dedifferentiation in culture" as required by the first independent claim of the instant application.

With regard to the claim rejection under 35 USC § 103 applicant argue the combined disclosures of Harris, Jauregui and Triglia do not disclose or suggest any immortalized hepatocytes that are stable in culture and do not undergo dedifferentiation in culture, a required

attribute of the claimed hepatocytes. This is not found persuasive as explained above with regard to Harris and Jauregui. Applicants also argue that the cell line disclosed by Triglia produces reduced amounts of albumin with increasing passages in culture. However, the meaning of claimed term "stable" in culture relates to the positive (or negative) expression of differentiation marker rather than to the amounts produced. In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Claims 31 and 32 , drawn to the cell lines Fa2N-4 (ATCC PTA-5566) and Ea1C-35 (ATCC PTA-5565), are free from prior art. Claims 31 and 32 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Vera Afremova whose telephone number is (571) 272-0914. The examiner can normally be reached from Monday to Friday from 9.30 am to 6.00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber, can be reached at (571) 272-0925.

The fax phone number for the TC 1600 where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Technology center 1600, telephone number is (571) 272-1600.

Vera Afremova

January 14, 2009

VERA AFREMOVA

PRIMARY EXAMINER

/Vera Afremova/
Primary Examiner, Art Unit 1657